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(54) Title: METAL SALTS OF CARNITINES, DIETARY SUPPLEMENTS CONTAINING SAME AND DIETARY KITS FOR COUNTERACING SEXUAL DISORDERS IN MALE SUBJECTS

(57) Abstract: Stable non -hygroscopic carnitine zinc citrates are disclosed, which favourably lend themselves to the preparation of both solid, orally administrable compositions and fluid compositions for dermatological use. Dietary supplements comprising the aforesaid salts are effective in enhancing sperm motility and count in sub-fertile subjects.

Metal salts of carnitines, dietary supplements containing same and dietary kits for counteracting sexual disorders in male subjects.

The present invention relates to novel metal salts of carnitines, dietary/nutritional supplements, drugs and dietary kits containing said salts.

More particularly, the present invention relates to the citrates of carnitines and zinc which are stable, non hygroscopic and water-soluble compounds. Therefore, these salts especially lend themselves to the production of both solid compositions suitable for oral administration and, owing to their water-solubility, to the formulation of liquid or fluid compositions, such as dermatological preparations, as described hereinbelow.

The present invention also relates to dietary/nutritional supplements and drugs comprising the aforesaid citrates which are effective in all those situations wherein zinc supplementation reverses or prevents the onset of the prejudicial effects brought about by zinc deficiency. These dietary/nutritional supplements are especially, although not exclusively, suitable to enhance sperm motility and concentration in the seminal fluid of sub-fertile males and treat idiopathic asthenospermia, owing to the joint action of carnitine, zinc and citrate.

The present invention further relates to dietary kits which contain doses of the aforesaid dietary supplements and doses of the aminoacid arginine. These kits are especially, even though not exclusively, effective for counteracting sexual disorders in male subjects.

In accordance with the present invention, with the term "carnitines" reference is collectively made herein to both L-carnitine and lower alkanoyl L-carnitines wherein the alkanoyl group, straight or branched-chain, contains 2-5 carbon atoms. This alkanoyl shall be concisely termed "(C_2-C_5) alkanoyl" hereinbelow.

With the term "non-hygroscopic" reference is herein made to the ability endowed by certain carnitine salts (particularly, those of the present invention) when they occur as powders or granules, to withstand a relative humidity of at least 60%, at 25°C, for 24 hours, without giving rise to adverse phenomena of clotting, agglomeration or even deliquescence which result in loss of their flowability.

With the term "hygroscopic" reference is herein made to the property shown by most carnitine salts (particularly by their "inner salts") to undergo when they occur as powders or granules, significant alteration of their flowability due to their clotting, agglomeration or even deliquescence, following exposure to an environnement of relative humidity lower than 50-60%, at 25°C, for 24 hours.

With the term "sexual disorders in male subjects" reference is collectively made herein to both male infertility brought about by inadequate sperm mobility and concentration in the seminal fluid and erectile dysfunctions, i.e. the difficulty or even inability to maintain an erect penis during sexual intercourse, a condition reported to affect 10 million American men and whose incidence is age-related (see Current Medical Diagnosis & Treatment, 38th Edition, page 911, 1999 by Appleton & Lange).

Carnitine citrates are already known. Carnitine citrate is disclosed in the UK patent 1,153,640 (Societè d'etudes de produits chimiques). L-carnitine and magnesium citrate and its utility in sports nutrition are disclosed in US patent 5,071,874 (Lonza Ltd.). Both these citrates are considerably hygroscopic.

The problems of storage and processing brought about by the high hygroscopicity of L-carnitine and alkanoyl L-carnitine inner salts have long since been known. This high hygroscopicity renders the manufacture and storage of orally administrable solid presentation forms particularly troublesome.

However, administration forms such as tablets and capsules represent the preferred presentation forms inasmuch as they make it particularly easy for users to take the active ingredient and comply with optimal dosage regimens.

The problem of L-carnitine and alkanoyl L-carnitine inner salts hygroscopicity has been satisfactorily solved by converting these inner salts into salts of pharmacologically acceptable acids, based on the assumption that such salts maintain the same therapeutical/ nutritional activities of the inner salts and do not exhibit unwanted toxic or side effects.

Although there is now an extensive body of literature, particularly patents, disclosing the production of allegedly stable, non-hygroscopic carnitine salts, actually only L-carnitine acid fumarate (US 4,602,039, Sigma-Tau) and L-carnitine L-(+)-tartrate (US 5,703,376, Lonza) have been developed on an industrial scale and marketed to date.

Carnitine and zinc deficiencies may bring about multiform disturbances.

For a detailed review of the various pathological consequences induced by carnitine and zinc deficiencies (which may be brought about by an insufficiently balanced diet: for instance, high milk consumption, poor in zinc, may be responsible for such deficit) reference is made to "The Merck Manual of Diagnosis and Therapy" 17th Edition (Centennial Edition), 1999, pages 32 and 53, whose contents is incorporated herein by reference.

With specific reference to the treatment of male infertility provoked by disturbances in sperm motility, inadequate sperm concentration in the seminal fluid and altered sperm morphology, the beneficial therapeutical effects achieved with the administration of L-carnitine (see, e.g., Vitali G. et al., Drugs Exptl. Clin. Res. XXI (4), 157-159, 1995; Costa M. et al., Andrologia, 26: 155-159,1994) and acetyl L-

carnitine (Moncada M.L. et al., Acta. Eur. Fertil. 23 (5) 221-224, 1992), have long since been known.

Finally, the US patent 6,090,848 discloses the unexpected synergistic effect on sperm motility and concentration in the seminal fluid of sub-fertile males, and the therapeutical effect in the treatment of idiopathic asthenospermia, achieved by administering a combination composition of L-carnitine/acetyl L-carnitine wherein their molar ratio is preferably about 3:1, in contrast with the monopharmacological treatment.

Recently, a number of nutritional therapies entailing the supplementation of the diet with mineral elements such as zinc and selenium have been shown to improve sperm motility and sperm count (see, e.g., S. Sinçlair, "Male infertility: Nutritional and environmental considerations", Altern. Med. Rev: 2000; 5(1), 28-38).

The human body contains 2 to 3 grams of zinc and in males a relevant part thereof is found in testes. The sign and symptoms of zinc deficiency include, among others, "delayed sexual maturation, hypogonadism and hypospermia" (The Merck Manual, loc. cit. page 53).

Zinc is an essential mineral for proper prostate gland function whose secretions comprise approximately 40% of seminal fluid wherein zinc levels are directly related to sperm motility and concentration.

Deficiency of dietary zinc reduces both sperm count and seminal plasma volume and results in delayed spermatozoal maturation and impaired sperm motility. Diet supplementation with zinc has been shown to reverse these phenomena.

Zinc contained in prostatic secretion of healthy males exerts a potent antibacterial action and thus prevents infections ascending from the urethra. Lower than normal zinc levels have been shown in prostatic secretions of males with bacterial prostatitis (see Current Medical Diagnosis & treatment, 38th Edition, 1999, page 900).

Citric acid, by aiding spermatozoa maturation and nourishment, is an essential component of the thick alkaline fluid secreted by the epithelium of the seminal vesicles, contributing to sperm total volume by about 60%.

The World Health Organization, in pointing out the normal and pathological values of the various parameters characterizing the seminal fluid of human beings, has fixed to 52 μm/ejaculate (sperm total amount of a single ejaculation) the minimum amount of citric acid needed to warrant an effective sperm motility following one hour after ejaculation (http://www.il-st-acad-sci.org/androl1.html). Citric acid concentrations lower than that previously indicated are generally liked to sub-fertility condition brought about by insufficient sperm motility and count.

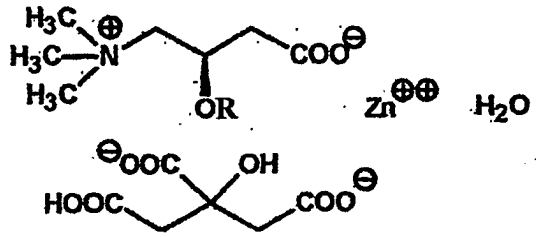
It is, therefore, felt the need to have available stable, non-hygroscopic and water-soluble carnitine and zinc citrates in order to allow the preparation of orally administrable especially, but not exclusively, solid compositions to be used as dietary/nutritional supplements in all those situation wherein zinc supplementation reverses or prevents the onset of prejudicial effects brought about by zinc deficiency.

Preferred dietary supplements because of the presence therein of salts which combine the efficacy of carnitine with that of zinc and citrate anion are those aimed at enhacing sperm motility and concentration and, consequently, improving the infertility conditions affecting sub-fertile male subjects.

It is furthermore advantageous, from an industrial viewpoint, that the aforesaid solid compositions can be prepared with conventional apparatuses and avoiding to resort to dehumidified facilities. This object can only be achieved if the aforesaid salts are stable and non-hygroscopic.

Moreover, in the light of the firmly established therapeutical properties of carnitines (such as, e.g., the protective action of L-carnitine on the cardiovascular system and in order to counteract or treat the pathological conditions induced by carnitine and zinc deficit ("The Merck Manual", loc.cit.), compositions comprising salts of zinc and carnitines can be advantageously used as drugs.

It has now been found that carnitine zinc citrates having formula (I)



(I)

wherein: R=hydrogen or straight or branched-chain (C_2-C_5) alkanoyl are stable, non-hygroscopic and water-soluble compounds which fully comply with the aforesaid prerequisites.

Preferred alkanoyls are acetyl, propionyl, butyryl, valeryl and isovaleryl.

It is surprising that the aforesaid citrates are non-hygroscopic in view of the considerable hygroscopicity of the only two known citrates, i.e. L-carnitine citrate and L-carnitine magnesium citrate.

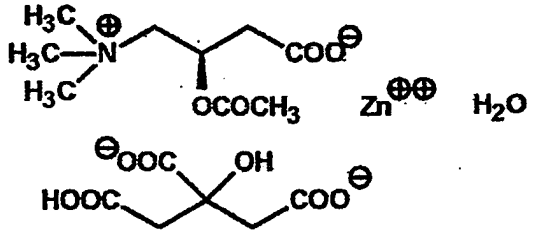
The following non-limiting examples show the preparation and main physico-chemical characteristics of some citrates of the present invention.

EXAMPLE 1
Acetyl L-carnitine zinc citrate

To a mixture of 21.1 g (0.1 moles) of 99% citric acid monohydrate, 20.3 g (0.1 moles) of acetyl L-carnitine inner salt and 22.0 g (0.1 moles) of zinc acetate dihydrate, 35 ml of water were added under stirring and heating to 30-35°C to aid the solubilization of the reagents. In a few minutes, a thick clear solution was obtained.

300 ml of acetone were added to the solution under vigorous stirring. After 100 ml of acetone were further added, the addition to the solution of a negligible amount of preformed salt as crystallization seed triggered the formation of a fine solid. In the absence of the crystallization seed, a pasty slurry firstly formed which turned, however, to a solid substance in a few minutes. Acetone was removed by decantation and to the residue 300 ml of the same solvent were added. The resulting mixture was vigorously stirred for 10-15 minutes, the solid thus obtained was filtered off and placed in an oven at 35°C for 4 hours and then at 55°C for 12 hours.

44.5 g (yield: 93,3%) of acetyl L-carnitine zinc citrate of formula



were obtained.

M.W. 476.74

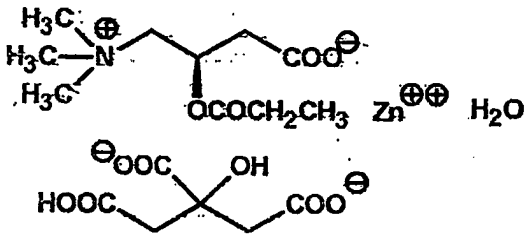
Calc.	C 37.79%;	H 5.29%;	N 2.94%;	Zn 13.71%
Found	C 37.69%;	H 5.30%;	N 2.92%;	Zn 13.51%

NMR (D_2O,δ,p.p.m.): 5.50 (m,1H, CH-O); 3.76 (m, 1H, CHH-N); 3.52

(m, 1H, CHH-N); 3.10 (s, 9H $(CH_3)_3$-N); 2.75 (dd, 2H, CH_2-COO/ALC); 2.60 (m, 4H $2CH_2$ COO/ac. citr.); 2.15 (m, 2H, CH_3-CH_2-CO); 1.05 (t, 3H, CH_3.CH_2-CCO).

EXAMPLE 2
Propionyl L-carnitine zinc citrate

The procedures of Example 1 were repeated by substituting 0.1 moles of propionyl L-carnitine inner salt for acetyl L-carnitine. The compound having the following formula was obtained with a yield of 95%:



M.W. 490.76

Calc.	C 39.16%;	H 5.55%;	N 2.85%;	Zn 13.32%
Found	C 39.36%;	H 5.50%;	N 2.78%;	Zn 13.20%

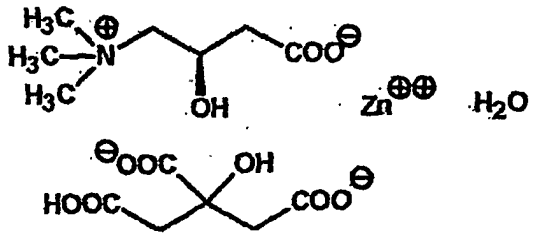
NMR (D_2O,δ,p.p.m.): 5.55 (m,1H, CH-O); 3.38 (m, 1H, CHH-N); 3.57 (m, 1H, CHH-N); 3.12 (s, 9H $(CH_3)_3$-N); 2.79 (dd, 2H, CH_2-COO/ALC) 2.61 (m, 4H $2CH_2$ COO/ac. citr.); 2.07 (s, 3H, CH_3-CO).

EXAMPLE 3
L-carnitine zinc citrate

The procedures of Example 1 were repeated starting from 16.1 g (0.1 moles) of L-carnitine inner salt.

The solidification of the compound thus obtained took a longer time than that of the compound of Example 1. However, by keeping on stirring the reaction mixture after the first acetone addition and using a crystallization seed of the pre-formed compound, a solid compound

which could be easily filtered off was obtained. Yield 88.3%.
The formula of the compound was:



M.W. 434.74

Calc.	C 35.92%;	H 5.33%;	N 3.22%;	Zn 15.04%
Found	C 36.00%;	H 5.30%;	N 3.18%;	Zn 14.91%

NMR (D_2O,δ,p.p.m.): 4.53 (m,1H, CH-O); 3.37 (m, 2H, CH_2-N); 3.10 (s, 9H, $(CH_3)_3$-N); 2.30-2.60 (m, 6H CH_2-COO/LC and 2CH_2-COO/citr. ac)

The present invention also relates to compositions which comprise as active ingredient one of the aforesaid carnitine zinc citrates and, optionally, at least one pharmacologically acceptable excipient.

The compositions can present themselves as pharmaceuticals, OTC compositions, nutritional supplements and dietary supplements.

The compositions according to the present invention can also comprise further nutritional or pharmacological active ingredients. In particular, the dietary/nutritional supplements suitable for enhancing sperm motility and concentration may comprise further pharmacologically acceptable salts of L-carnitine and/or acetyl L-carnitine and/or propionyl L-carnitine.

Particularly preferred pharmacologically acceptable salts of L-carnitine are the acid fumarate, the tartrate and the galactarate. Those of acetyl L-canitine are the chloride, the acid fumarate and galactarate.

The compositions can also comprise fillers, binders, lubricants, mold release agents, flow-regulating agents, dispersing agents, colorants, flavoring agents and the like as it will be apparent to any expert in pharmaceutical technology or pharmacy.

As regards their therapeutic applications in the stricter sense of the word, the aforesaid carnitine and zinc citrates can be advantageously used, owing to their water-solubility, for manufacturing topically applicable, dermatological preparations, such as ointments, lotions and creams. In fact, the water-soluble zinc salts have long since been known to be effective against a variety of viruses, particularly those which bring about skin disorders, such as e.g. the herpes simplex viruses, HSV-1 and HSV-2. Because of this activity, L-carnitine zinc citrate can be effectively compounded in the lubricants for the external genital organs disclosed in US patent 5,208,031 (which is incorporated herein by reference.

The orally administrable, solid forms comprise tablets, chewable tablets, pills, troches, lozenges, capsules, powders or granulates. In case of powders or granulates the presentation form can occur as sachets.

Since zinc's Recommended Dietary Allowance (RDA) is 12-15 mg/day for adults (Goodman and Gilman's, "The Pharmacological Basis of Therapeutics", Eight Edition, 1990, page 1525) the compositions of the present invention, in unit dosage form, suitably contain the whole zinc's RDA, i.e. 12-15 mg, or a lower amount (from about 1/3 to about 1/2 of RDA) such as e.g. about 4-8 mg of zinc as carnitine zinc citrate for those individuals who stay on a multiple dose administration regimen.

15 mg of zinc are contained in 100 mg of L-carnitine zinc citrate, in 109 mg of acetyl L-carnitine zinc citrate and 113 mg of propionyl L-carnitine zinc citrate, respectively.

The aforesaid dietary/nutritional supplements of the present invention can also suitably comprise a selenium compound (e.g. selenomethionine), vitamins (e.g. vitamin C, vitamin E, vitamin B6, vitamin B12 and folic acid), coenzymes (e.g. coenzyme Q_{10}), ferulic acid and citric acid.

At least half the selenium in the male body is found in the semen. Recent studies indicate that reduced daily selenium intake due to an unbalanced diet may be linked to an increased risk of male infertility. A connection between selenium and sperm production has been reported. Selenium potent anti-oxidant activity in combination with vitamin E has long since been known.

Since selenium RDA is 55-57 μg/day (for adults) (see Goodman and Gilman's, loc. cit.), it is advantageous that the compositions of the invention in unit dosage form also comprise about 20-35 μg/day of selenium (preferably as selenomethionine). For instance, 70 μg of selenomethionine contain 28 μg of selenium.

As it will be apparent to any expert in pharmaceutical technology or pharmacy, the compositions for sachets may comprise suitable excipients such as fructose, citric acid, saccharin sodium, tonic water flavour, D-mannitol and colloidal silicon dioxide.

The compositions for tablets and chewable tablets may comprise excipients such as mint essence, saccharin sodium, sorbitol solution, sorbitol, magnesium stearate, talc, pregelatinized corn starch, mannitol and saccharose.

Thanks to the stability and non-hygroscopicity of the aforesaid salts of L-carnitine and alkanoyl L-carnitines, the compositions for capsules can be entirely free of excipients, in view of the chemical inertness of the ingredients towards the gelatinous material the capsules are made of.

Some non-limiting examples of compositions for dietary supplements in unit dosage form are given hereinbelow, wherein all the carnitine salts are non-hygroscopic and, therefore, lend themselves to the production not only of sachets, but also tablets, chewable tablets, pills, troches, lozenges and capsules.

Composistion 1

L-carnitine zinc citrate	33-50 mg (Zn ~ 5-7.5 mg)
or	
acetyl L-carnitine zinc citrate	36-55 mg (Zn ~ 5-7.5 mg)
a pharmacologically acceptable salt of L-carnitine (LC) or acetyl L-carnitine (ALC)	balance to 2-3 g

Composition 2

L-carnitine zinc citrate	33-50 mg (Zn ~ 5-7.5 mg)
or	
acetyl L-carnitine zinc citrate	36-55 mg (Zn ~ 5-7.5 mg)
a mixture of a pharmacologically acceptable salt of L-carnitine (LC) and a pharmacologically acceptable salt of acetyl L-carnitine (ALC) wherein the LC/ALC molar ratio is from 4:1 to 1:1	balance to 2-3 g

Composition 3

L-carnitine zinc citrate	33-50mg (Zn ~ 5-7 mg)

L-carnitine acid fumarate	1.5-1.8 g
acetyl L-carnitine acid fumarate	0.4-0.6 g

Composition 4

L-carnitine zinc citrate	33-50 mg (Zn ~ 5-7 mg)
L-carnitine acid fumarate	1.5-1.8 g
acetyl L-carnitine acid fumarate	0.4-0.6 g

Composition 5

Anyone of the preceding compositions further comprising at least one of the follo ingredients:

selenomethionine	4-70 μg
coenzyme Q_{10}	80-100 mg
Vitamin E	5-15 mg
ferulic acid	10-15 mg
lipoic acid	20-50 mg
citric acid	50-100 mg

The present invention finally relates to a dietary kit which comprises:

a) at least one first container containing a dose of L-carnitine zinc citrate and a dose of a further pharmacologically acceptable salt of L-carnitine; and

b) at least one second container containing a dose of arginine.

According to a further embodiment of the aforesaid kit, the first container further contains a pharmacologically acceptable salt of acetyl L-carnitine, the LC/ALC molar ratio ranging from 4:1 to 1:1. The preferred LC/ALC molar ratio is about 3.

According to a still further embodiment, the kit comprises:

a1) at least one first container containing acetyl L-carnitine zinc citrate and a further pharmacologically acceptable salt of acetyl L-carnitine; and

b1) at least one second container containing arginine.

Container a1) can further contain a pharmacologically acceptable salt of L-carnitine, the molar ratio LC/ALC ranging from 4:1 to 1:4.

According to a still further embodiment, the first container a) or a1) can also contain a pharmacologically acceptable salt of propionyl L-carnitine (PLC), the molar ratio LC/ALC/PLC ranging from 4:1:0.5 to 1:4:2.

Preferred examples of pharmacologically acceptable salts of L-carnitine, acetyl L-carnitine and propionyl L-carnitine have been previously indicated.

During the last years, arginine-containing dietary supplements have become increasingly widespread because not only the nutritionally oriented doctors but also cardiologists and endocrinologists have ascertained the valuable therapeutic properties of this aminoacid.

It is known that arginine selectively lowers LDL cholesterol without reducing the beneficial HCL cholesterol and does so without producing unwanted side effects. It also promotes coronary micro-circulation and inhibits the formation of blood clots, a key etiological factor leading to heart attacks and strokes.

Arginine is a precursor/modulator of nitric oxide (NO). NO plays essential physiological roles which range from neurotransmission to vasodilation.

By relaxing arteries, NO can improve inadequate circulation-related conditions such as angina, intermittent claudication, hypertension and impaired brain circulation. NO is, moreover, the decisive factor in a man's ability to achieve and maintain an erection during sexual intercourse. Administration of 3 grams of arginine/day was reported to be effective in the treatment of erectile failure and impotence.

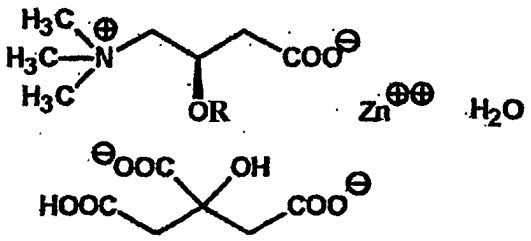
On the grounds of the previous disclosures, the users who particularly – although not exclusively – may benefit from the kit of the present invention are those male consumers who are in need of both improving their ability to achieve and maintain an erection during sexual intercourse and enhancing sperm motility and count in the seminal fluid.

For instance, the first container may contain any one of the preceding compositions 1-5, and the second container 1.0-2.0 g of arginine. It is advisable that the contents of a first container and the contents of a second container are ingested by the user substantially at the same time, twice-three times a day.

To avoid arginine's risk of promoting free radical oxidation, it is advisable that the arginine container also contains an antioxidant which can be selected from a broad spectrum of known antioxidants. Preferred examples of antioxidants are coenzyme Q_{10} and lipoic acid.

What is claimed is:

1. Carnitine zinc citrate of formula (I)



(I)

wherein R is hydrogen or straight or branched-chain (C_2-C_5) alkanoyl.

2. The citrate of claim 1 wherein the (C_2-C_5) alkanoyl is selected from the group consisting of acetyl, propionyl, butyryl, valeryl and isovaleryl.

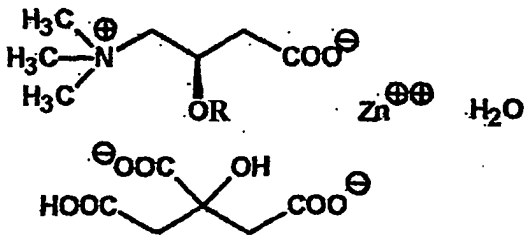
3. L-carnitine zinc citrate as citrate of claim 1.

4- Acetyl L-carnitine zinc citrate as citrate of claim 2.

5. Propionyl L-carnitine zinc citrate as citrate of claim 2.

6. A composition comprising

(a) a carnitine zinc citrate of formula (I)



(I)

wherein R is hydrogen or straight or branched chain (C_2-C_5) alkanoyl; and optionally

(b) a pharmacologically acceptable excipient.

7. A dietary supplement which, in unit dosage form, comprises:

L-carnitine zinc citrate	33-50 mg (Zn~ 5-7.5 mg)
a pharmacologically acceptable salt of L-carnitine (LC) or acetyl L-carnitine (ALC)	balance to 2-3 g

8. A dietary supplement which, in unit dosage form, comprises:

acetyl L-carnitine zinc citrate	36-55 mg (Zn~ 5-7.5 mg)
a pharmacologically acceptable salt of L-carnitine (LC) or acetyl L-carnitine (ALC)	balance to 2-3 g

9. A dietary supplement which, in unit dosage form, comprises:

L-carnitine zinc citrate	33-50 mg (Zn~ 5-7.5 mg)
a mixture of a pharmacologically acceptable salt of L-carnitine (LC) and a pharmacologically acceptable salt of acetyl L-carnitine (ALC) wherein the LC/ALC molar ratio is from 4:1 to 1:1	balance to 2-3 g

10. A dietary supplement which, in unit dosage form, comprises:

acetyl L-carnitine zinc citrate	36-55 mg (Zn~ 5-7.5 mg)
a mixture of a pharmacologically acceptable salt of L-carnitine (LC) and a pharmacologically acceptable salt of acetyl L-carnitine (ALC) wherein the LC/ALC molar ratio is from 4:1 to 1:1	balance to 2-3 g

11. The dietary supplement of claim 7 or 9, wherein the pharmacologically acceptable salt of L-carnitine is selected from the group comprising the tartrate, the acid fumarate and the galactarate of L-carnitine.

12. The dietary supplement of claim 8 or 10 wherein the pharmacologically acceptable salt of acetyl L-carnitine is selected from the group comprising the chloride, the acid fumarate and the galactarate of acetyl L-carnitine.

13. The dietary supplement of claim 9, which, in unit dosage form, comprises:

L-carnitine zinc citrate	33-50 mg (Zn~ 5-7 mg)
L-carnitine acid fumarate	1.5-1.8 g
acetyl L-carnitine acid fumarate	0.4-0.6 g

14. The dietary supplement of claim 10 which, in unit dosage form, comprises:

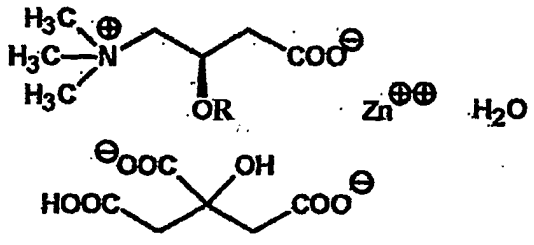
acetyl L-carnitine citrate	36-55 mg (Zn~ 5-7.5 mg)
L-carnitine acid fumarate	1.5-1.8 g
acetyl L-carnitine acid fumarate	0.4-0.6 g

15. The dietary supplement of any one of the claims 7-14, which further comprises at least one of the following ingredients:

selenomethionine	4-70 μg
coenzyme Q_{10}	80-100 mg
Vitamin E	5-15 mg
ferulic acid	10-15 mg
lipoic acid	20-50 mg
citric acid	50-100 mg

16. A dietary kit which comprises:

(a) at least one first container containing a carnitine zinc citrate of formula (I)



(I)

wherein R is hydrogen or a straight or branched-chain (C_2-C_5) alkanoyl and

a further carnitine salt selected from the group consisting of the pharmacologically acceptable salts of L-carnitine, acetyl L-carnitine,

propionyl L-carnitine or mixtures thereof; and

(b) at least one second container containing arginine.

17. The kit of claim 16, wherein the mixture of the pharmacologically acceptable salts comprises L-carnitine (LC) and acetyl L-carnitine (ALC) wherein the LC/ALC molar ratio is from 4:1 to 1:4.

18. The kit of claim 16 wherein the mixture of the pharmacologically acceptable salts comprises L-carnitine (LC), acetyl L-carnitine (ALC) and propionyl L-carnitine (PLC), wherein the LC/ALC/PLC molar ratio is from 4:1:0.5 to 1:4:2.

19. The kit of claims 16-18 wherein the pharmacologically acceptable salts of L-carnitine is selected from the group comprising the tartrate, acid fumarate and galactarate of L-carnitine and the pharmacologically acceptable salt of acetyl L-carnitine or propionyl L-carnitine is selected from the group comprising the chloride, acid fumarate and galactarate of acetyl L-carnitine.

20. The kit of claims 17 and 19, wherein the first container contains

L-carnitine zinc citrate	33-50 mg (Zn~ 5-7.5 mg)
a mixture of pharmacologically acceptable salts of L-carnitine and acetyl L-carnitine	balance to 2-3 g

and the second container contains

arginine	1-2 g

21. The kit of claims 17 and 19, wherein the first container contains

acetyl L-carnitine zinc citrate	36-55 mg (Zn~ 5-7.5 mg)
a mixture of pharmacologically acceptable salts of L-carnitine and acetyl L-carnitine	balance to 2-3 g

and the second container contains

arginine	1-2 g

22. An antiherpetic dermatological preparation comprising a carnitine zinc citrate of claims 1-5, in a concentration effective to hinder the conveyance of the herpes simplex viruses HSV-1 and/or HSV-2 from an infected subject to a healty one.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C229/22 C07C229/76 A23L1/304 A61K31/315 A23L1/30
A61K35/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 058693 A (FASSI ALDO) 1 August 2002 (2002-08-01) the whole document	1-21
P,X	US 2002/142052 A1 (TRANT) 3 October 2002 (2002-10-03) the whole document	1-21
Y	US 5 071 874 A (SCHOLL THOMAS ET AL) 10 December 1991 (1991-12-10) the whole document	1-21
Y	US 2001/027214 A1 (SCAFETTA ET AL.) 4 October 2001 (2001-10-04) the whole document	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2003	30/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lorenzo Varela, M.J.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 5 952 379 A (FASSI ALDO) 14 September 1999 (1999-09-14) the whole document	1-21
Y	US 6 271 258 B1 (FASSI ALDO) 7 August 2001 (2001-08-07) *abstract; column 2, lines 51-67; column 3; the claims and the examples*	1-21
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Y	EP 0 628 308 A (AVANTGARDE SPA) 14 December 1994 (1994-12-14) *abstract and the claims*	22
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